| | L # | Hits | Search Text | DBs | Time Stamp |
|---|---|---|---|---|---|
| 1 | L1 | 327 | methionine adj aminopeptidase$ | USPAT; US-PGPUB | 2003/08/01 10:32 |
| 2 | L2 | 5548 | (methionine or met) same muta$10 | USPAT; US-PGPUB | 2003/08/01 10:33 |
| 3 | L3 | 147 | 1 same 2 | USPAT; US-PGPUB | 2003/08/01 10:33 |

US-PAT-NO: 6403076

DOCUMENT-IDENTIFIER: US 6403076 B1

TITLE: Compositions for increasing hematopoiesis with interleukin-3 mutants

DATE-ISSUED: June 11, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Bauer; S. Christopher | New Haven | MO | 63068 | N/A |
| Abrams; Mark Allen | St. Louis | MO | 63130 | N/A |
| Braford-Goldberg; Sarah Ruth | St. Louis | MO | 63108 | N/A |
| Caparon; Marie Helena | Chesterfield | MO | 63017 | N/A |
| Easton; Alan Michael | Maryland Heights | MO | 63146 | N/A |
| Klein; Barbara Kure | St. Louis | MO | 63131 | N/A |
| McKearn; John Patrick | Glencoe | MO | 63038 | N/A |
| Olins; Peter Q | Glencoe | MO | 63038 | N/A |
| Paik; Kumnan | Ballwin | MO | 63021 | N/A |
| Thomas; John Warren | Town & Country | MO | 63131 | N/A |


APPL-NO: 08/ 468683

DATE FILED: June 6, 1995

PARENT-CASE:

This is a divisional of U.S. Ser. No. 08/191,973, filed Feb. 4, 1994, now U.S. Pat. No. 5,772,992; and is a continuation-in-part of U.S. Ser. No. 08/411,796, filed Apr. 6, 1995, now U.S. Pat. No. 5,677,149; which is a 371 of PCT/US93/11198, filed Nov. 22, 1993; which is a continuation-in-part of U.S. Ser. No. 07/981,044, filed Nov. 24, 1992, now abandoned.

US-CL-CURRENT: 424/85.2, 424/85.1 , 514/2 , 530/351

ABSTRACT:

The present invention relates to human interleukin-3 (hIL-3) variant or mutant proteins (muteins) functionally co-administered with a other colony stimulating factors (CSF), cytokines, lymphokines, interleukins, hematopoietic growth factors or IL-3 variants.

22 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX (31):

Suitable cells or cell lines for the production of the proteins claimed in the present invention may be bacterial cells. For example, the various strains of E. coli are well-known as host cells in the field of biotechnology. Examples of such strains include E. coli strains JM101 [Yanish-Perron, et al. (1985)] and MON105 [Obukowicz, et al. (1992)]. Also included in the present invention is the expression of the IL-3 variant protein utilizing a chromosomal expression vector for E. coli based on the bacteriophage Mu (Weinberg et al., 1993). Various strains of B. subtilis may also be employed as host cells for expression of the polypeptides of the present invention. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the polypeptides of the present invention. When expressed in the E. coli cytoplasm, the above-mentioned **mutant** hIL-3 variants of the present invention may also be constructed with **Met**-Ala- at the N-terminus so that upon expression the **Met** is cleaved off leaving Ala at the N-terminus. The IL-3 variant proteins of the present invention may include polypeptides having **Met**-, Ala- or **Met**-Ala- attached to the N-terminus. When the IL-3 variant polypeptides are expressed in the cytoplasm of E. coli, polypeptides with and without **Met** attached to the N-terminus are obtained. The N-termini of proteins made in the cytoplasm of E. coli are affected by posttranslational processing by **methionine aminopeptidase** (Ben-Bassat et al., 1987) and possibly by other peptidases. These IL-3 variant proteins may also be expressed in E. coli by fusing a signal peptide to the N-terminus. This signal peptide is cleaved from the polypeptide as part of the secretion process. Secretion in E. coli can be used to obtain the correct amino acid at the N-terminus (e.g., Asn.sup.15 in the (15-125) hIL-3 polypeptide) due to the precise nature of the signal peptidase. This is in contrast to the heterogeneity which may be observed at the N-terminus of proteins expressed in the cytoplasm in E. coli.

US-PAT-NO: 6130318

DOCUMENT-IDENTIFIER: US 6130318 A

TITLE: hIL-4 mutant proteins used as antagonists or partial agonists of human interleukin 4

DATE-ISSUED: October 10, 2000


INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Wild; Hanno | Wuppertal | N/A | N/A | DE |
| Hanko; Rudolf | Dusseldorf | N/A | N/A | DE |
| Dorschug; Michael | Heiligenhaus | N/A | N/A | DE |
| Horlein; Hans-Dietrich | Wuppertal | N/A | N/A | DE |
| Beunink; Jurgen | Wuppertal | N/A | N/A | DE |
| Apeler; Heiner | Wuppertal | N/A | N/A | DE |
| Wehlmann; Hermann | Wuppertal | N/A | N/A | DE |
| Sebald; Walter | Wurzburg | N/A | N/A | DE |



APPL-NO: 08/ 765012

DATE FILED: December 19, 1996

FOREIGN-APPL-PRIORITY-DATA:

| COUNTRY | APPL-NO | APPL-DATE |
|---|---|---|
| DE | 44 23 131 | July 1, 1994 |

PCT-DATA:
APPL-NO: PCT/EP95/02358
DATE-FILED: June 19, 1995
PUB-NO: WO96/01274
PUB-DATE: Jan 18, 1996
371-DATE: Dec 19, 1996
102(E)-DATE:Dec 19, 1996

US-CL-CURRENT: 530/351, 424/85.1 , 424/85.2



ABSTRACT:

The present invention relates to novel hIL-4 mutant proteins, to processes for preparing them, and to their use as medicaments, in particular in overshooting, falsely regulated immune reactions and autoimmune diseases.


12 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX (94):

In order to prepare an IL-4 mutein which lacks the N-terminal **methionine,** an amino acid was inserted, in position (+2), which leads to the elimination of the N-terminal **methionine,** in E. coli, by means of a specific **methionine aminopeptidase** (Flinta et al., Eur. J. Biochem. 15, 193-196, 1986). For this, the vector RPR9-IL4-Y 124D (enclosure 1) was cut with the restriction endonucleases XhoI and BamHI. The resulting DNA fragment of approx. 450 bp in length, which carries the sequence information for the IL4Y124D gene and a short (approx. 50 bp) fragment from the atpE region of the vector, was purified by agarose gel electrophoresis and recloned into the vector M13mp18, which had been cut with SalI and BamHI. Single-stranded DNA was prepared and subjected to an in-vitro **mutagenesis** reaction using the following oligonucleotide:

| | Document ID | Issue Date | Pages | Title |
|---|---|---|---|---|
| 1 | US 20030144228 A1 | 20030731 | 74 | PON3 and uses thereof |
| 2 | US 20030143680 A1 | 20030731 | 13 | Descendants of bacteria devoid of N terminal formylation useful for the production of proteins and peptides |
| 3 | US 20030143595 A1 | 20030731 | 72 | Hedgehog interacting proteins and uses related thereto |
| 4 | US 20030119729 A1 | 20030626 | 77 | METHOD OF TREATING DOPAMINERGIC AND GABA-NERGIC DISORDERS |
| 5 | US 20030108916 A1 | 20030612 | 58 | Cloning and functional assays of Xenopus ATR |
| 6 | US 20030105002 A1 | 20030605 | 104 | RGS compositions and therapeutic and diagnostic uses therefor |
| 7 | US 20030104995 A1 | 20030605 | 64 | Neuroprotective methods and compositions |
| 8 | US 20030104970 A1 | 20030605 | 70 | Regulation of epithelial tissue by hedgehog-like polypeptides, and formulations and uses related thereto |
| 9 | US 20030100489 A1 | 20030529 | 59 | Cell-cycle regulatory proteins, and uses related thereto |
| 10 | US 20030097676 A1 | 20030522 | 113 | Plant acyl-CoA synthetases |
| 11 | US 20030097666 A1 | 20030522 | 274 | Novel human genes and gene expression products:II |
| 12 | US 20030083242 A1 | 20030501 | 83 | METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING PERIPHERAL NEUROPATHIES |

| | Document ID | Issue Date | Pages | Title |
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| 13 | US 20030082620 A1 | 20030501 | 59 | Novel human genes and gene expression products: II |
| 14 | US 20030077587 A1 | 20030424 | 68 | Glaucoma therapeutics and diagnostics |
| 15 | US 20030077288 A1 | 20030424 | 42 | Compositions and methods for treatment of muscle wasting |
| 16 | US 20030073116 A1 | 20030417 | 97 | ADAMTS13 genes and proteins and variants, and uses thereof |
| 17 | US 20030068831 A1 | 20030410 | 47 | Proteins and druggable regions of proteins |
| 18 | US 20030068651 A1 | 20030410 | 49 | Multi-target analysis of gene families for chemistry of high affinity and selective small molecules and other therapeutics |
| 19 | US 20030068650 A1 | 20030410 | 48 | Target analysis for chemistry of specific and broad spectrum anti-infectives and other therapeutics |
| 20 | US 20030054437 A1 | 20030320 | 121 | VERTEBRATE EMBRYONIC PATTERN-INDUCING PROTEINS AND USES RELATED THERETO |
| 21 | US 20030037357 A1 | 20030220 | 104 | Plant acyl-CoA synthetases |
| 22 | US 20030028915 A1 | 20030206 | 38 | Acyl coenzyme a thioesterases |
| 23 | US 20030022170 A1 | 20030130 | 59 | Novel fibroblast growth factors and therapeutic and diagnostic uses therefor |
| 24 | US 20020197616 A1 | 20021226 | 175 | Nod2 nucleic acids and proteins |
| 25 | US 20020182701 A1 | 20021205 | 46 | Dominant negative variants of methionine aminopeptidase 2 (MetAP2) and clinical uses thereof |
| 26 | US 20020160375 A1 | 20021031 | 36 | Human Patched genes and proteins, and uses related thereto |
| 27 | US 20020156239 A1 | 20021024 | 40 | EPH receptor ligands, and uses related thereto |

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| 28 | US 20020151460 A1 | 20021017 | 72 | REGULATION OF EPITHELIAL TISSUE BY HEDGEHOG-LIKE POLYPEPTIDES, AND FORMULATIONS AND USES RELATED THERETO |
| 29 | US 20020146773 A1 | 20021010 | 65 | "Signalin" family of TGFbeta signal transduction proteins, and uses related thereto |
| 30 | US 20020144298 A1 | 20021003 | 50 | Novel human genes and gene expression products |
| 31 | US 20020127687 A1 | 20020912 | 17 | Genome DNA of bacterial symbiont of aphids |
| 32 | US 20020127673 A1 | 20020912 | 90 | Nod2 nucleic acids and proteins |
| 33 | US 20020088015 A1 | 20020704 | 64 | WILMS' TUMOR WT1 BINDING PROTEINS |
| 34 | US 20020082410 A1 | 20020627 | 34 | Insulin promoter factor, and uses related thereto |
| 35 | US 20020082392 A1 | 20020627 | 62 | ANTIBODIES TO CELL-CYCLE REGULATORY PROTEINS, AND USES RELATED THERETO |

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| 36 | US 20020045206 A1 | 20020418 | 77 | VERTEBRATE EMBRYONIC PATTERNING-INDUCING PROTEINS, COMPOSITIONS AND USES RELATED THERTO |
| 37 | US 20020034758 A1 | 20020321 | 50 | Novel human genes and gene expressions products: II |
| 38 | US 20020032323 A1 | 20020314 | 64 | STREPTOCOCCUS PNEUMONIAE POLYNUCLEOTIDES AND SEQUENCES |
| 39 | US 20020025569 A1 | 20020228 | 44 | COMPONENTS OF UBIQUITIN LIGASE COMPLEXES AND USES RELATED THERETO |
| 40 | US 20020025305 A1 | 20020228 | 54 | CELL-CYCLE REGULATORY PROTEINS, AND USES RELATED THERETO |
| 41 | US 20010047078 A1 | 20011129 | 10 | Methods for identifying inhibitors of methionine aminopeptidases |
| 42 | US 20010041353 A1 | 20011115 | 36 | Novel SSP-1 compositions and therapeutic and diagnostic uses therefor |
| 43 | US 6593454 B2 | 20030715 | 11 | Methods for identifying inhibitors of methionine aminopeptidases |
| 44 | US 6593104 B1 | 20030715 | 58 | Macular degeneration diagnostics and therapeutics |
| 45 | US 6576237 B1 | 20030610 | 120 | Vertebrate tissue pattern-inducing proteins, and uses related thereto |
| 46 | US 6573370 B1 | 20030603 | 73 | PON3 and uses thereof |
| 47 | US 6518411 B1 | 20030211 | 101 | RGS compositions and therapeutic and diagnostic uses therefor |

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| 48 | US 6514724 B1 | 20030204 | 69 | Hedgehog interacting proteins and uses related thereto |
| 49 | US 6509152 B1 | 20030121 | 59 | Immunosuppressant target proteins |
| 50 | US 6503742 B1 | 20030107 | 47 | Ubiquitin ligases and uses related thereto |
| 51 | US 6486131 B2 | 20021126 | 54 | Cell-cycle regulatory proteins, and uses related thereto |
| 52 | US 6479261 B1 | 20021112 | 288 | Methods of using interleukin-3 (IL-3) mutant polypeptides for ex-vivo expansion of hematopoietic stem cells |
| 53 | US 6464974 B1 | 20021015 | 57 | Immunosuppressant target proteins |
| 54 | US 6458931 B1 | 20021001 | 314 | Interleukin-3 (IL-3) multiple mutation polypeptides |
| 55 | US 6436677 B1 | 20020820 | 54 | Method of reverse transcription |
| 56 | US 6428977 B1 | 20020806 | 61 | Signalin family of TGF.beta. signal transduction proteins, and uses related thereto |
| 57 | US 6403307 B1 | 20020611 | 68 | Glaucoma therapeutics and diagnostics |
| 58 | US 6403076 B1 | 20020611 | 86 | Compositions for increasing hematopoiesis with interleukin-3 mutants |

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| 59 | US 6399760 B1 | 20020604 | 53 | RP compositions and therapeutic and diagnostic uses therefor |
| 60 | US 6399349 B1 | 20020604 | 120 | Human aminopeptidase P gene |
| 61 | US 6399326 B1 | 20020604 | 51 | Nucleic acids encoding neural/pancreatic receptor tyrosine phosphatase |
| 62 | US 6395526 B1 | 20020528 | 38 | DNA polymerase |
| 63 | US 6384192 B1 | 20020507 | 118 | Vertebrate embryonic pattern-inducing proteins |
| 64 | US 6379662 B1 | 20020430 | 112 | Co-administration of interleukin-3 mutant polypeptides with CSF's for multi-lineage hematopoietic cell production |
| 65 | US 6361977 B1 | 20020326 | 264 | Methods of using multivariant IL-3 hematopoiesis fusion protein |
| 66 | US 6361976 B1 | 20020326 | 130 | Co-administration of interleukin-3 mutant polypeptides with CSF'S for multi-lineage hematopoietic cell production |
| 67 | US 6331390 B1 | 20011218 | 65 | Cell-cycle regulatory proteins, and uses related thereto |
| 68 | US 6309879 B1 | 20011030 | 36 | Human patched genes and proteins, and uses related thereto |

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| 69 | US 6306586 B1 | 20011023 | 62 | Methods and compositions for the diagnosis and treatment of cataracts |
| 70 | US 6296853 B1 | 20011002 | 43 | E6 binding proteins |
| 71 | US 6274342 B1 | 20010814 | 39 | Nucleic acid molecules encoding monocyte chemotactic protein 5 (MCP-5) molecules and uses therefor |
| 72 | US 6271363 B1 | 20010807 | 119 | Nucleic acids encoding hedgehog proteins |
| 73 | US 6271026 B1 | 20010807 | 45 | Glaucoma compositions |
| 74 | US 6268476 B1 | 20010731 | 37 | EPH receptor ligands, and uses related thereto |
| 75 | US 6262334 B1 | 20010717 | 259 | Human genes and expression products: II |
| 76 | US 6262333 B1 | 20010717 | 381 | Human genes and gene expression products |

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| 77 | US 6261794 B1 | 20010717 | 9 | Methods for identifying inhibitors of methionine aminopeptidases |
| 78 | US 6261786 B1 | 20010717 | 128 | Screening assays for hedgehog agonists and antagonists |
| 79 | US 6225456 B1 | 20010501 | 50 | Ras suppressor SUR-5 |
| 80 | US 6211334 B1 | 20010403 | 67 | Cell-cycle regulatory proteins, and uses related thereto |
| 81 | US 6207450 B1 | 20010327 | 54 | Glaucoma therapeutics and diagnostics based on a novel human transcription factor |
| 82 | US 6197945 B1 | 20010306 | 33 | Insulin promoter factor, and uses related thereto |
| 83 | US 6194556 B1 | 20010227 | 77 | Angiotensin converting enzyme homolog and therapeutic and diagnostic uses therfor |
| 84 | US 6171798 B1 | 20010109 | 32 | P53-regulated genes |
| 85 | US 6165747 A | 20001226 | 120 | Nucleic acids encoding hedgehog proteins |
| 86 | US 6153183 A | 20001128 | 131 | Co-administration of interleukin-3 mutant polypeptides with CSF's or cytokines for multi-lineage hematopoietic cell production |

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| 87 | US 6150137 A | 20001121 | 60 | Immunosuppressant target proteins |
| 88 | US 6147192 A | 20001114 | 48 | Tub interactor (TI) polypeptides and uses therefor |
| 89 | US 6143491 A | 20001107 | 46 | Therapeutic compositions and methods and diagnostic assays for type II diabetes involving HNF-1 |
| 90 | US 6132991 A | 20001017 | 87 | Human interleukin-3 (IL-3) variant fusion proteins |
| 91 | US 6130318 A | 20001010 | 21 | hIL-4 mutant proteins used as antagonists or partial agonists of human interleukin 4 |
| 92 | US 6127521 A | 20001003 | 60 | Immunosuppressant target proteins |
| 93 | US 6127158 A | 20001003 | 32 | Ubiquitin conjugating enzymes |
| 94 | US 6121045 A | 20000919 | 70 | Human Delta3 nucleic acid molecules |
| 95 | US 6093395 A | 20000725 | 141 | Co-administration of interleukin-3 mutant polypeptides with CSF's for multi-lineage hematopoietic cell production |
| 96 | US 6087107 A | 20000711 | 54 | Therapeutics and diagnostics for congenital heart disease based on a novel human transcription factor |
| 97 | US 6074639 A | 20000613 | 90 | Ex vivo expansion of hematopoietic cells using interleukin-3 (IL-3) variant fusion proteins |

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| 98 | US 6068982 A | 20000530 | 73 | Ubiquitin conjugating enzymes |
| 99 | US 6066318 A | 20000523 | 321 | Multi-functional hematopoietic fusion proteins between sequence rearranged C-MPL receptor agonists and other hematopoietic factors |
| 100 | US 6060262 A | 20000509 | 40 | Regulation of I Kappa B (I.kappa.B) degradation and methods and reagents related thereto |
| 101 | US 6060047 A | 20000509 | 122 | Co-administration of interleukin-3 mutant polypeptides with CSF's for multi-lineage hematopoietic cell production |
| 102 | US 6057427 A | 20000502 | 66 | Antibody to cytokine response gene 2(CR2) polypeptide |
| 103 | US 6057133 A | 20000502 | 113 | Multivariant human IL-3 fusion proteins and their recombinant production |

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| 104 | US 6051398 A | 20000418 | 71 | Nucleic acids encoding CR3 polypeptide, vector and transformed cell thereof, and expression thereof |
| 105 | US 6046308 A | 20000404 | 55 | Isolated TRBP polypeptides and uses therefor |
| 106 | US 6043030 A | 20000328 | 62 | Cell-cycle regulatory proteins, and uses related thereto |
| 107 | US 6037173 A | 20000314 | 55 | Isolated nucleic acid encoding TRBP |
| 108 | US 6031076 A | 20000229 | 43 | Conservin compositions |
| 109 | US 6030812 A | 20000229 | 257 | Fusion proteins comprising multiply mutated interleukin-3 (IL-3) polypeptides and second growth factors |
| 110 | US 6027914 A | 20000222 | 72 | Nucleic acids encoding CR6 polypeptide vector and transformed cell thereof, and expression thereof |
| 111 | US 6022535 A | 20000208 | 276 | Treatment of hematopoietic disorders with fusion proteins comprising multiply mutated interleukin-3 (IL-3) polypeptides and second growth factors |
| 112 | US 6020155 A | 20000201 | 72 | Nucleic acids encoding CR1 fusion protein, vector, transfected cell and expression |
| 113 | US 6020135 A | 20000201 | 33 | P53-regulated genes |

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| 114 | US 6015692 A | 20000118 | 32 | CDC37 cell-cycle regulatory protein and uses related thereto |
| 115 | US 6008014 A | 19991228 | 47 | Method of making lipid metabolic pathway compositions |
| 116 | US 6001619 A | 19991214 | 49 | Ubiquitin ligases, and uses related thereto |
| 117 | US 5997860 A | 19991207 | 79 | Ex-vivo expansion of stem cells using combinations of interleukin-3 (IL-3) variants and other cytokines |
| 118 | US 5997857 A | 19991207 | 114 | Co-administration of interleukin-3 mutants with colony stimulating factors |
| 119 | US 5989804 A | 19991123 | 42 | E6 binding proteins |
| 120 | US 5981702 A | 19991109 | 35 | Cyclin/CDK associated proteins, and uses related thereto |
| 121 | US 5981699 A | 19991109 | 85 | Human ubiquitin conjugating enzyme |
| 122 | US 5968821 A | 19991019 | 52 | Cell-cycle regulatory proteins, and uses related thereto |
| 123 | US 5968761 A | 19991019 | 61 | Ubiquitin conjugating enzymes |

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| 124 | US 5962316 A | 19991005 | 52 | Cell-cycle regulatory proteins, and uses related thereto |
| 125 | US 5955306 A | 19990921 | 64 | Genes encoding proteins that interact with the tub protein |
| 126 | US 5912326 A | 19990615 | 38 | Cerebellum-derived growth factors |
| 127 | US 5912141 A | 19990615 | 41 | Nucleic acids encoding tumor virus susceptibility genes |
| 128 | US 5889169 A | 19990330 | 32 | Cell cycle regulatory protein p16 gene |
| 129 | US 5885776 A | 19990323 | 43 | Glaucoma compositions and therapeutic and diagnositic uses therefor |
| 130 | US 5882894 A | 19990316 | 69 | Nucleic acids encoding CR8 polypeptides, vector and transformed cell thereof, and expression thereof |
| 131 | US 5871961 A | 19990216 | 72 | Nucleic acids encoding CR2 polypeptides, vector and transformed cell thereof, and expression thereof |
| 132 | US 5871960 A | 19990216 | 73 | Nucleic acids encoding CR5 polypeptide, vector and transformed cell thereof, and expression thereof |

| | Document ID | Issue Date | Pages | Title |
|---|---|---|---|---|
| 133 | US 5849989 A | 19981215 | 33 | Insulin promoter factor, and uses related thereto |
| 134 | US 5844079 A | 19981201 | 111 | Vertebrate embryonic pattern-inducing proteins, and uses related thereto |
| 135 | US 5821051 A | 19981013 | 33 | E6 binding proteins |
| 136 | US 5807708 A | 19980915 | 42 | Conservin nucleic acid molecules and compositions |
| 137 | US 5800998 A | 19980901 | 36 | Assays for diagnosing type II diabetes in a subject |
| 138 | US 5795734 A | 19980818 | 53 | EPH receptor ligands, and uses related thereto |
| 139 | US 5795726 A | 19980818 | 47 | Methods for identifying compounds useful in treating type II diabetes |
| 140 | US 5792833 A | 19980811 | 48 | E2 binding proteins |
| 141 | US 5772992 A | 19980630 | 89 | Compositions for co-administration of interleukin-3 mutants and other cytokines and hematopoietic factors |
| 142 | US 5770384 A | 19980623 | 49 | Method for determining compound interaction with E2 binding proteins |
| 143 | US 5756671 A | 19980526 | 32 | CDC37 cell-cycle regulatory protein, and uses related thereto |

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| 144 | US 5744343 A | 19980428 | 75 | Ubiquitin conjugating enzymes |
| 145 | US 5738849 A | 19980414 | 87 | Interleukin-3 (IL-3) variant fusion proteins, their recombinant production, and therapeutic compositions comprising them |
| 146 | US 5691147 A | 19971125 | 62 | CDK4 binding assay |
| 147 | US 5136023 A | 19920804 | 8 | Polypeptide with cell-spreading activity |

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FILE 'HOME' ENTERED AT 11:25:33 ON 01 AUG 2003

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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
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11 FILES IN THE FILE LIST

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FILE 'MEDLINE'
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         10438 AMINOPEPTIDASE#
L1         125 METHIONINE AMINOPEPTIDASE#
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FILE 'LIFESCI'
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L15         12 L3 AND MUTA?

FILE 'BIOTECHDS'
         34971 MUTA?
L16         10 L4 AND MUTA?

FILE 'BIOSIS'
        460569 MUTA?
L17         25 L5 AND MUTA?

FILE 'EMBASE'
        337260 MUTA?
L18         20 L6 AND MUTA?

FILE 'HCAPLUS'
        422485 MUTA?
L19         42 L7 AND MUTA?

FILE 'NTIS'
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L20          0 L8 AND MUTA?

FILE 'ESBIOBASE'
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L21         18 L9 AND MUTA?

FILE 'BIOTECHNO'
        230455 MUTA?
L22         18 L10 AND MUTA?

FILE 'WPIDS'
         21845 MUTA?
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L23           6 L11 AND MUTA?

TOTAL FOR ALL FILES
L24         220 L12 AND MUTA?

=> s l24 not 2001-2003/py
FILE 'MEDLINE'
       1333217 2001-2003/PY
L25          20 L13 NOT 2001-2003/PY

FILE 'SCISEARCH'
       2436064 2001-2003/PY
L26          37 L14 NOT 2001-2003/PY

FILE 'LIFESCI'
        233279 2001-2003/PY
L27          11 L15 NOT 2001-2003/PY

FILE 'BIOTECHDS'
         50027 2001-2003/PY
L28           7 L16 NOT 2001-2003/PY

FILE 'BIOSIS'
       1289472 2001-2003/PY
L29          21 L17 NOT 2001-2003/PY

FILE 'EMBASE'
       1118376 2001-2003/PY
L30          16 L18 NOT 2001-2003/PY

FILE 'HCAPLUS'
       2550709 2001-2003/PY
L31          28 L19 NOT 2001-2003/PY

FILE 'NTIS'
         36116 2001-2003/PY
L32           0 L20 NOT 2001-2003/PY

FILE 'ESBIOBASE'
        709813 2001-2003/PY
L33          15 L21 NOT 2001-2003/PY

FILE 'BIOTECHNO'
        301474 2001-2003/PY
L34          16 L22 NOT 2001-2003/PY

FILE 'WPIDS'
       2387168 2001-2003/PY
L35           1 L23 NOT 2001-2003/PY

TOTAL FOR ALL FILES
L36         172 L24 NOT 2001-2003/PY

=> dup rem l36
PROCESSING COMPLETED FOR L36
L37          64 DUP REM L36 (108 DUPLICATES REMOVED)

=> d tot

L37  ANSWER 1 OF 64  SCISEARCH  COPYRIGHT 2003 THOMSON ISI on STN
TI   Identification of critical residues in the active site of porcine
     membrane-bound aminopeptidase P
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L37 ANSWER 3 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI The biochemical and molecular characterization of recombinant Bacillus subtilis tripeptidase (PepT) as a zinc-dependent metalloenzyme
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L37 ANSWER 4 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
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L37 ANSWER 5 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Novel effects of a transposon insertion in the Vibrio fischeri glnD gene: defects in iron uptake and symbiotic persistence in addition to nitrogen utilization
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L37 ANSWER 7 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
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TI Erratum: Yeast **methionine aminopeptidase** I. Alteration of substrate specificity by site-directed **mutagenesis** (Journal of Biological Chemistry (1999) 274 (13403-13409)).
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L37 ANSWER 9 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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L37 ANSWER 10 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
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TI Cloning and expression of genes for unmodified recombinant human adult hemoglobin production
SO U.S., 21 pp.
CODEN: USXXAM
IN Ho, Chien; Shen, Tong-jian
AN 1998:324789 HCAPLUS
DN 129:1443

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5753465 | A | 19980519 | US 1994-298339 | 19940830 |

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AN 1997246025 ESBIOBASE
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E-mail: s-tsunas@mx.biwa.or.jp
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CODEN: JOBIAO ISSN: 0021-924X
DT Journal; Article
CY Japan
LA English
SL English

L37 ANSWER 31 OF 64 MEDLINE on STN DUPLICATE 11
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L37 ANSWER 41 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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L37 ANSWER 44 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
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L37 ANSWER 47 OF 64 MEDLINE on STN DUPLICATE 17
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L37 ANSWER 48 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
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AN 1992:422435 HCAPLUS
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L37 ANSWER 49 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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AN 93136711 MEDLINE

L37 ANSWER 51 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI DOES UNCONTROLLED SURVIVAL OF ACETYLATED PEPTIDES LEAD TO CELL-PROLIFERATION - DELETION OF N-TERMINAL DEACETYLATING SYSTEM FOR PROTEIN PEPTIDE IN SMALL-CELL LUNG-CARCINOMA CELLS
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ISSN: 0022-2143.
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AN 92:635176 SCISEARCH

L37 ANSWER 52 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
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L37 ANSWER 53 OF 64 LIFESCI COPYRIGHT 2003 CSA on STN
TI Cloning and nucleotide sequence of the Salmonella typhimurium pepM gene.
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L37 ANSWER 54 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
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DN 114:75950

L37 ANSWER 55 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
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PI EP 311228 12 Apr 1989

L37 ANSWER 56 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
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SO Gene; (1988) 65, 1, 13-22
CODEN: GENED6
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L37 ANSWER 57 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
TI Cloning E. coli genes by oligonucleotide hybridization;
Escherichia coli
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L37 ANSWER 58 OF 64 MEDLINE on STN DUPLICATE 21
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L37 ANSWER 59 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
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L37 ANSWER 60 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
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AN 1987-12132 BIOTECHDS

L37 ANSWER 61 OF 64 MEDLINE on STN DUPLICATE 22
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Journal code: 2985121R. ISSN: 0021-9258.
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L37 ANSWER 62 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI AMINO-TERMINAL PROCESSING OF **MUTANT** FORMS OF YEAST ISO-1-CYTOCHROME-C - THE SPECIFICITIES OF **METHIONINE AMINOPEPTIDASE** AND ACETYLTRANSFERASE
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L37 ANSWER 63 OF 64 MEDLINE on STN DUPLICATE 23
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L37 ANSWER 64 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Identification and **mutational** relocation of the AUG codon initiating translation of iso-1-cytochrome c in yeast
SO Journal of Biological Chemistry (1971), 246(24), 7429-45
CODEN: JBCHA3; ISSN: 0021-9258
AU Stewart, John W.; Sherman, Fred; Shipman, Nancy A.; Jackson, Mary
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DN 76:11934

=> d ab 11,23, 24

L37 ANSWER 11 OF 64 MEDLINE on STN DUPLICATE 3
AB In eukaryotes, two isozymes (I and II) of **methionine aminopeptidase** (MetAP) catalyze the removal of the initiator methionine if the penultimate residue has a small radius of gyration (glycine, alanine, serine, threonine, proline, valine, and cysteine). Using site-directed **mutagenesis**, recombinant yeast MetAP I derivatives that are able to cleave N-terminal methionine from substrates that have larger penultimate residues have been expressed. A Met to Ala change at 329 (Met206 in Escherichia coli enzyme) produces an average catalytic efficiency 1.5-fold higher than the native enzyme on normal substrates and cleaves substrates containing penultimate asparagine, glutamine, isoleucine, leucine, methionine, and phenylalanine. Interestingly, the native enzyme also has significant activity with the asparagine peptide not previously identified as a substrate. **Mutation** of Gln356 (Gln233 in E. coli MetAP) to alanine results in a catalytic efficiency about one-third that of native with normal substrates but which can cleave methionine from substrates with penultimate histidine, asparagine, glutamine, leucine, methionine, phenylalanine, and tryptophan. **Mutation** of Ser195 to alanine had no effect on substrate specificity. None of the altered enzymes produced cleaved substrates with a fully charged residue (lysine, arginine, aspartic acid, or glutamic acid) or tyrosine in the penultimate position.

L37 ANSWER 23 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AB We describe a T7-based Escherichia coli expression vector in which protein coding sequence is seamlessly fused to the N-terminal calmodulin-binding peptide (CBP) purification tag. We combined the use of the site-specific protease enterokinase (EK) and the type IIs restriction enzyme Eam1104 I, which cleave outside their respective (amino acid and nucleotide) target sequences, such that any amino acid sequence may be fused directly C-terminal to the EK cleavage site without codon constraints conferred by the cloning method. PCR products are cloned using ligation-dependent or ligation-independent methods with high cloning efficiencies (>10(6) cfu/mu g vector), allowing production of insert

quantities sufficient for several cloning experiments with a limited number of PCR cycles, resulting in a significant time-savings and reduced likelihood of accumulating PCR-derived **mutations**. CBP fusion proteins are expressed to high levels when the CBP peptide is positioned at the N-terminus. CBP binds to calmodulin with nanomolar affinity, and fusion proteins are purified to near homogeneity from crude extracts with one pass through calmodulin affinity resin using gentle binding and elution conditions. We show high efficiency seamless cloning of three inserts into the pCAL-n-EK vector, including one encoding the protein c-Jun N-terminal kinase (JNK). CBP-EK-JNK fusion protein was synthesized to 10-20 mg/liter culture and purified to near homogeneity in one step wit calmodulin affinity resin. The fusion tag was efficiently removed wit EK to yield active JNK wit native N-terminal amino acid sequence. (C) 1999 Academic Press.

L37 ANSWER 24 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN

AB Methods for obtaining unmodified recombinant human normal adult Hb A (rHb A) involve a novel expression plasmid that coexpressessu human .alpha.- and .beta.-globin genes and Escherichia coli **methionine aminopeptidase** genes under the control of sep. tac promoters. Methods are also provided for correcting an abnormal conformation of some of the heme groups incorporated in the proteins expressed by the expression plasmid. **Methionine aminopeptidase** cleaves the N-terminal methionines on the Hb A so that the mol. that is produced does not contain N-terminal methionines. The rHb A can be used as a component of a blood substitute or therapeutic agent, and the expression system can produced rHb A in high yield and also can be modified to produce **mutant** Hbs that are desired for therapeutic uses. Expression vector pHE2 which is used to express rHb A in E. coli is also claimed.

=> d ab 30, 34, 42, 43

L37 ANSWER 30 OF 64 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V. on STN

AB A gene for a **methionine aminopeptidase** (MAP; EC 3.4.11.18), which catalyzes the removal of amino-terminal methionine from the growing peptide chain on the ribosome, has been cloned from the hyperthermophilic Archaeon, Pyrococcus furiosus, by a novel method effectively using its cosmid protein library, sequenced and expressed in Escherichia coli. The DNA sequence encodes a protein containing 295 amino acid residues with methionine at the N-terminus. From protein analyses of the recombinant protein expressed in E. coli, by using both amino acid sequence analysis from the N-terminus by automated Edman degradation and analyses of molecular masses of the peptides generated by two enzymatic cleavages performed independently, digestions with lysylendopeptidase and Endoproteinase Asp-N, with ionspray mass spectrometry, the primary structure of the protein has been elucidated to be completely identical with that deduced from its DNA sequence. Comparison of the amino acid sequence of P. furiosus MAP (P.f. MAP) with those of other MAPs from Eukarya and Bacteria showed that the protein has a high degree of sequence homology in the stretches surrounding the five cobalt-binding residues fully preserved in all of MAPs determined so far, but P.f. MAP belongs to Type II because it has an extra long insertion of about 60 amino acid residues between the fourth and fifth cobalt-binding ligands, similar to MAPs from human and rat, and to Met-AP2 from Saccharomyces cerevisiae in comparison to Type I MAPs from Bacteria. Therefore, P.f. MAP seems to be rather close to those from Eukarya, although it is distinct in lacking the N-terminal extension of about 90-150 residues universally found in MAPs from Eukarya. These findings suggest that P.f. MAP is evolutionally located at the Eukarya-Bacteria boundary. The enzyme expressed in E. coli exhibits a considerable thermostability, with a half-life of approximately 4.5 h at 90.degree.C and an optimum temperature of around 90.degree.C.

L37 ANSWER 34 OF 64 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB A full-length recombinant human apolipoprotein C-II (ApoC-II) has been successfully expressed in Escherichia coli using the T7 expression system. The recombinant ApoC-II, which was expressed intracellularly in the inclusion bodies, was solubilized with 8 M urea and purified using Sephadex G-75 gel permeation chromatography. Four liters of the bacterial culture yielded 16-20 mg of purified recombinant ApoC-II. Sequencing and mass spectrometric analyses indicated that the isolated recombinant ApoC-II contained predominantly (64%) the native form with threonine as the N-terminus, but also contained a minor (36%) molecular form of ApoC-II with an additional methionine at the N-terminus (Met-ApoC-II), Analysis of the recombinant ApoC-II by tryptic digestion and high performance liquid chromatography-electrospray mass spectrometry provides additional conclusive evidence that, with the exception of the N-terminus of Met-ApoC-II, the expressed ApoC-II has the expected peptide sequence. However, this extra N-terminal methionine residue can be excised by further in vitro treatment with **methionine aminopeptidase**. The purified recombinant ApoC-II was found to be competent in the activation of bovine milk lipoprotein lipase. Thus, the recombinant ApoC-II prepared from E. coli may have a pharmacological application for the treatment of patients with genetic hypertriglyceridemia caused by ApoC-II deficiency.

L37 ANSWER 42 OF 64 MEDLINE on STN

AB Human immunodeficiency virus (HIV) reverse transcriptase isolated from viral particles contains two subunits, p51 and p66. We have produced both subunits in separate Escherichia coli strains using expression vectors. Stop codons were placed immediately after the codon for the carboxyl-terminal residue of the mature processed p51 and p66 subunits found in viral particles. Insertion of a methionine in front of the HIV protease cleavage site in the recombinant protein enabled synthesis of both subunits with the natural amino-terminal proline, since E. coli **methionine aminopeptidase** cleaves a Met-Pro amino-terminal linkage. That this occurred to an extent greater than 95% was confirmed by sequencing the purified subunits. Examination of the activities of the individual p51 and p66 subunits on a variety of templates and under solution conditions optimized for each subunit revealed a significant catalytic activity for the natural p51 subunit. This result contrasts to results reported earlier for many recombinant forms without the natural amino and/or carboxyl termini. As expected from earlier work, the optimal homopolymeric template for the p66 subunit was poly(rA). For the p51 subunit, poly(dC) was found to be the optimal template; its activity is 2- to 4-fold greater than p66 on poly(dC). The p51 subunit is 13- to 50-fold less active on poly(rC). These findings are discussed in the context of our earlier hypothesis (McHenry, C. S. (1989) in Molecular Biology of Chromosome Function (Adolph, K., ed) Chap. 5, Springer-Verlag, New York) that the HIV reverse transcriptase might be functionally asymmetric with distinct plus- and minus-strand polymerases.

L37 ANSWER 43 OF 64 MEDLINE on STN DUPLICATE 16

AB We have constructed a plasmid (pHE2) in which the synthetic human alpha- and beta-globin genes and the **methionine aminopeptidase** (Met-AP) gene from Escherichia coli are coexpressed under the control of separate tac promoters. The Hbs were expressed in E. coli JM109 and purified by fast protein liquid chromatography, producing two major components, a and b. Electrospray mass spectrometry shows that at least 98% and about 90% of the expressed alpha and beta chains of component a, respectively, have the expected masses. The remaining 10% of the beta chain in component a corresponds in mass to the beta chain plus methionine. In component b, both alpha and beta chains have the correct masses without detectable N-terminal methionine (< 2%). These results have been confirmed by Edman degradation studies of the amino-terminal sequences of the alpha and beta chains of these two recombinant Hb (rHb)

samples. rHbs from components a and b exhibit visible optical spectra identical to that of human normal adult Hb (Hb A). Component a and Hb A have very similar oxygen-binding properties, but component b shows somewhat altered oxygen binding, especially at low pH values. 1H-NMR spectra of component a and Hb A are essentially identical, whereas those of component b exhibit altered ring current-shifted and hyperfine-shifted proton resonances, indicating altered heme conformation in the beta chain. These altered resonance patterns can be changed to those of Hb A by converting component b to the ferric state and then to the deoxy state and finally back to either the carbonmonoxy or oxy form. Thus, our E. coli expression system produces native, unmodified Hb A in high yield and can be used to produce desired **mutant** Hbs.

=> d ab 47,48,50,52,56-61

L37 ANSWER 47 OF 64 MEDLINE on STN DUPLICATE 17

AB A **methionine aminopeptidase** that specifically removes methionine residues from peptides with amino-terminal sequences of Met-Ala-, Met-Val-, Met-Ser-, Met-Gly-, and Met-Pro- but not Met-Leu- or Met-Lys- has been isolated to homogeneity from porcine liver by a procedure involving five chromatographic steps. The enzyme, whose specificity matches that predicted for the entity responsible for the co-translational amino-terminal processing of nascent polypeptide chains, has a measured molecular mass of 70,000 Da by SDS-polyacrylamide electrophoresis and 67,000 Da by gel chromatography (under nondenaturing conditions), suggesting the native molecule is a monomer. It is activated by Co2+ and inhibited by beta-mercaptoethanol and EDTA. With octapeptide substrates related to the amino-terminal portion of the beta-chain of human hemoglobin (with a histidine in position 3), the enzyme had a pH optimum of 6.0. With a synthetic peptide devoid of histidine, it showed no pH dependence from 6.0 to 8.0. This sensitivity may be due to the propensity of peptides with histidine in the third position to bind divalent cations such as Co2+. The measured Km and kappa cat values were affected by residues in the second position. The peptide corresponding to the natural sequence (Met-Val-His-) gave a kappa cat/Km value of 260 mM-1 s-1; substitution of alanine in the second position raised the kappa cat/Km to 1523 mM-1 s-1, but substitution of proline lowered the value to 130. The effects are primarily on the kappa cat. The substitution of proline (for histidine) in the third position, the **mutation** found in hemoglobin Long Island, prevents the removal of the methionine residue, as occurs with the **mutant** protein. The porcine liver enzyme is similar to **methionine aminopeptidases** isolated from Escherichia coli, Salmonella typhimurium, and yeast in that it also is stimulated by Co2+. However, it is much larger than these enzymes and differs somewhat in specificity, particularly with the yeast enzyme.

L37 ANSWER 48 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN

AB A yeast gene for a **methionine aminopeptidase**, one of the central enzymes in protein synthesis, was cloned and sequenced. The DNA sequence encodes a precursor protein contg. 387 amino acid residues. The mature protein, whose NH2-terminal sequence was confirmed by Edman degrdn., consists of 377 amino acids. The function of the 10-residue sequence at the NH2 terminus, contg. 1 serine and 6 threonine residues, remains to be established. In contrast to the structure of the prokaryotic enzyme, the yeast **methionine aminopeptidase** consists of 2 functional domains: a unique NH2-terminal domain contg. 2 motifs resembling zinc fingers, which may allow the protein to interact with ribosomes, and a catalytic COOH-terminal domain resembling other prokaryotic **methionine aminopeptidases**. Furthermore, unlike the case for the prokaryotic gene, the deletion of the yeast MAP1 gene is not lethal, suggesting for the first time that alternative NH2-terminal processing pathway(s) exist for cleaving methionine from

nascent polypeptide chains in eukaryotic cells.

L37 ANSWER 50 OF 64 MEDLINE on STN DUPLICATE 18
AB A synthetic gene encoding the Group II phospholipase A2 (PLA2) from the venom of Agkistrodon piscivorus piscivorus has been constructed and expressed with high efficiency in Escherichia coli. No enzymatic activity was recovered when the polypeptide contained the initiator Met residue. Replacement of an Asn residue penultimate to the initiator Met with Ser or Gly permitted removal of the initiator Met by the endogenous **methionine aminopeptidase**. The amino-terminal serine (N-Ser) and amino-terminal glycine PLA2's were isolated from intracellular inclusion bodies and were renatured with 25% recovery. Automated Edman degradation confirmed the removal of the initiator Met and confirmed the sequence of the first 40 residues of N-Ser PLA2. The recombinant proteins were purified to apparent homogeneity and showed the same specific activity as the wild-type protein. N-Ser PLA2 demonstrated the same kinetics of activation as the wild type enzyme on large vesicles of zwitterionic lipid.

L37 ANSWER 52 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AB Genetic engineering can complement traditional methods to improve fermentation processes with the aim of reducing production costs. Selected examples in which genetic engineering techniques were used to improve fermentation processes were described. Example 1: fermentation of corn starch to ethanol, where the fermentation rate of soluble starch by recombinant Saccharomyces cerevisiae strains containing the Aspergillus awamori glucoamylase (EC-3.2.1.3) gene was controlled by the glucoamylase activity. Improved rates of starch fermentation were achieved using recombinant strains utilizing maltose and possessing a higher glucoamylase activity. Example 2: removal of the initiation methionine from recombinant proteins using **methionine-aminopeptidase** produced by recombinant Escherichia coli. Example 3: higher expression of recombinant proteins with low acetic acid producing **mutants** due to higher cell density fermentations, higher production rates and increased product concentration. Example 4: genetic methods to improve cellulose production by Acetobacter **mutants** defective in glucose-dehydrogenase (EC-1.1.1.47). (3 ref)

L37 ANSWER 56 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AB A human granulocyte colony stimulating factor (CSF) gene was cloned in Escherichia coli MM294 using plasmid pHCW701 (containing a trpP promoter, to generate plasmid pPD2), or plasmid pFC54.t (containing a pL promoter, to generate plasmid pJD1) as expression vector. Expression in E. coli was improved by alteration of the 5' sequence of the gene by site-directed **mutagenesis**. Initially, no mRNA or protein was detected in the trpP system, and only mRNA was detected in the pL system. When the G+C content was decreased at the 5' end, without altering the predicted protein sequence, mRNA and protein were detected in both systems. Expression reached 17% and 6.5% of total soluble cellular protein in the pL and trpP expression systems, respectively. The N-terminal sequence of the recombinant granulocyte CSF from the pL system was Met-Thr-Pro-Leu-Gly-Pro. Granulocyte CSF isolated from a human LD-1 cell culture did not have an N-terminal methionine residue. Deletion of the threonine codon at the start of the gene for the mature protein resulted in efficient removal of the methionine residue during expression in E. coli. (34 ref)

L37 ANSWER 57 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AB A 3.5 kbp PstI fragment carrying the whole gene coding for the Escherichia coli **methionine-aminopeptidase** (map) which contains 2.3 kbp of the 5' region was cloned. A total PstI genomic digest of C600 DNA (30 ug) was electrophoresed on an agarose gel. Fragments of 3-4.5 Kbp were electroeluted from gel slices and ligated to

PstI-cut replicative form of M13mp19. Standard hybridizing procedures were used to identify plaques hybridizing with a synthetic 30-mer oligonucleotide probe corresponding to the first 10 codons of map. Recombinant phages were 50% larger than the wild-type M13mp19 phages and were stable. Oligonucleotide hybridization provides a very efficient way to clone homologous genes in E. coli JM105 when a partial amino acid sequence of the product is known, particularly when no characterized **mutation** can be used in a complementation test. (8 ref)

L37 ANSWER 58 OF 64 MEDLINE on STN DUPLICATE 21
AB Polypeptides synthesized in the cytoplasm of eukaryotes are generally initiated with methionine, but N-terminal methionine is absent from most mature proteins. Many proteins are also N alpha-acetylated. The removal of N-terminal methionine and N alpha-acetylation are catalyzed by two enzymes during translation. The substrate preferences of the **methionine aminopeptidase** (EC 3.4.11.x) and N alpha-acetyltransferase (EC 2.3.1.x) have been partially inferred from the distribution of amino-terminal residues and/or **mutations** found for appropriate mature proteins, but with some contradictions. In this study, a synthetic gene corresponding to the mature amino acid sequence of the plant protein thaumatin, expressed in yeast as a nonexported protein, i.e., lacking a signal peptide, has been used to delineate the specificities of these enzymes with respect to the penultimate amino acid. Site-directed **mutagenesis**, employing synthetic oligonucleotides, was utilized to construct genes encoding each of the 20 amino acids following the initiation methionine codon, and each protein derivative was isolated and characterized with respect to its amino-terminal structure. All four possible N-terminal variants--those with and without methionine and those with and without N alpha-acetylation--were obtained. These results define the specificity of these enzymes in situ and suggest that the nature of the penultimate amino-terminal residue is the major determinant of their selectivity.

L37 ANSWER 59 OF 64 HCAPLUS COPYRIGHT 2003 ACS on STN
AB Crude exts. of a multiply peptidase-deficient strain of S. typhimurium contain an aminopeptidase that specifically removes N-terminal methionine from peptides. This activity shows pronounced specificity for the peptide's 2nd amino acid; methionine is removed from peptides with alanine, threonine, or glycine in the 2nd position but not from those in which the 2nd amino acid is leucine or methionine. The activity is stimulated by Co2+ and is inhibited by EDTA. **Mutations** that lead to overprodn. (up to 30-fold) of the activity were obtained by selecting for growth on Met-Gly-Gly as a methionine source. These **mutations** map at .apprx.3 map units, and are phage P22 cotransducible with leu. The overproducer **mutations** are dominant to wild type, and duplication of the wild-type allele of the locus leads to a gene dosage effect on peptidase levels. This suggests that the locus of the overproducer **mutations** may be the structural gene for the peptidase. SDS-PAGE shows an increased level of a single protein of 34 kilodaltons in the overproducer **mutant**. This protein is highly enriched in a purified prepn. of the peptidase. The specificity of this enzyme suggests that it is involved in the cleavage of methionine from newly synthesized peptide chains. Treatment of purified unprocessed interleukin 1.beta. (contg. N-terminal methionine) with the purified peptidase results in removal of N-terminal methionine with no addnl. alterations. Thus N-terminal processing of at least this protein can occur after translation is complete. This enzyme was named peptidase M (methionine-specific aminopeptidase).

L37 ANSWER 60 OF 64 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AB Computer analyses of about 100 chemically determined amino-terminal sequences of Escherichia coli proteins allowed the classification of N-terminal sequences into 2 categories, corresponding to processed and non-processed polypeptide chains. From this analysis, a molecular

enzymatic model was deduced, accounting for the occurrence or non-occurrence of the maturation proces, and consistent with the existence of a unique enzyme. According to the model, the excision of the initiator methionyl residue would take place only when the accessible area of the lateral chain of the 2nd amino acid is inferior to 147 Az. To examine the model, systematic substitution was performed on the 2nd amino acid of methionyl-tRNA-synthetase (EC-6.1.1.10) by site-directed **mutagenesis**. A shuttle vector based on protein fusion with beta-galactosidase was designed to facilitate rapid **mutant** protein purification and N-terminal microsequencing. Experimental results were in agreement with the proposed model, and confirmed prediction based on the model concerning amino acids not yet found in the 2nd position in bacterial proteins. (0 ref)

L37 ANSWER 61 OF 64 MEDLINE on STN DUPLICATE 22

AB Amino-terminal processing in the yeast Saccharomyces cerevisiae has been investigated by examining numerous **mutationally** altered forms of iso-1-cytochrome c. Amino-terminal residues of methionine were retained in sequences having penultimate residues of arginine, asparagine, glutamine, isoleucine, leucine, lysine, and methionine; in contrast, the amino-terminal methionine residues were exercised from residues of alanine, glycine, and threonine and were partially excised from residues of valine. The results suggest the occurrence of a yeast aminopeptidase that removes amino-terminal residues of methionine when they precede certain amino acids. A systematic search of the literature for amino-terminal sequences formed at initiation sites suggests the hypothetical yeast aminopeptidase usually has the same specificity as the amino peptidase from bacteria and higher eukaryotes. Our results and the results from the literature search suggest that the aminopeptidase cleaves amino-terminal methionine when it precedes residues of alanine, glycine, proline, serine, threonine, and valine but not when it precedes residues of arginine, asparagine, aspartic acid, glutamine glutamic acid, isoleucine, leucine, lysine, or methionine. In contrast to the normal iso-1-cytochrome c and in contrast to the majority of the **mutationally** altered proteins, certain forms were acetylated including the following sequences: acetyl(Ac)-Met-Ile-Arg-, Ac-Met-Ile-Lys, Ac-Met-Met-Asn-, and Ac-Met-Asn-Asn-. We suggest yeast contains acetyltransferases that acetylates these **mutant** forms of iso-1-cytochromes c because their amino-terminal regions resemble the amino-terminal regions of natural occurring proteins which are normally acetylated. The lack of acetylation of closely related sequences suggest that the hypothetical acetyltransferases are specific for certain amino-terminal sequences and that the 3 amino-terminal residues may play a critical role in determining these specificities.

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